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(54) HEMOFILTRATION AND PLASMAFILTRATION DEVICE

VORRICHTUNG ZUR HÄMOFILTRATION UND PLASMAFILTRATION

DISPOSITIF D'HEMOFILTRATION ET DE PLASMAFILTRATION

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Description

[0001] This invention generally relates to devices for extracorporeally treating blood or blood fractions such as blood filtrate or plasma to selectively remove toxins therefrom.

[0002] By way of background, extensive efforts have been made to discover safe and effective methods for removing toxins from patients by extracorporeal treatment of their blood. These efforts have included many studies directed to methods for extracorporeal treatment of hepatic failure due to infection, cirrhosis, toxin damage or other causes. US-A-5 011 607 is concerned with the dialysis of blood to remove small soluble toxins and middle molecular weight molecules by using a device to affect bi-directional flow of fluid across a membrane. Many other methods have been proposed with the goal of removing small molecular toxins, protein-bound molecules or larger molecules thought to be responsible for the coma and illness of hepatic failure. Thus far, evidence has been presented supporting adverse effects caused by non-protein bound small molecules such as ammonia, phenols, mercaptans, short chain fatty acids, aromatic amino-acids, neural inhibitors (GABA, glutamate), false neural transmitters (octopamine) and bile salts. Among these, phenols and mercaptans, along with bilirubin and bacterial endotoxins, also occur as strong protein-bound toxins and are thus more difficult to effectively remove from the blood. In addition, there are a variety of middle molecular weight toxins of liver failure having molecular weights of about 300 to about 10,000 which are difficult to effectively remove.

[0003] As to specific modes of treatment, those previously proposed and used have included blood perfusion over heterogeneous liver pieces or past membranes which contact hepatocytes. Also proposed and used have been hemoperfusion through columns of coated activated carbon or macroreticular resins, blood exchange, plasmapheresis with plasma replacement, plasmapheresis with plasma perfusion through bilirubin-binding and aromatic amino acid-binding sorbents, standard hemodialysis, standard hemodialysis with an amino acid dialysate and plasma exchange, high permeability hemodialysis, dialysis with charcoal-impregnated membranes, continuous hemofiltration, peritoneal dialysis, oral sorbents and many other therapies.

[0004] While some of these previously proposed treatments have produced neurological improvement in stage 2 or 3 coma and have aided hepatic regeneration after injury, they have not provided much clinical improvement in patients in stage 4 coma on respirators. Additionally, these diverse treatments each produce adverse effects on the patient, offsetting benefits. See, generally, Ash, S.R., Treatment of Acute Hepatic Failure with Encephalopathy: A Review, Int. J. of Artif. Organs, Vol. 14, pp. 191-195 (1991).

[0005] For example, although daily charcoal hemoperfusion has been shown to provide neurologic and physiologic improvement of patients with hepatic failure and coma, Winchester, J.F., Hemoperfusion, in Replacement of Renal Function by Dialysis (Maher, J.F., ed.), Dordrecht:Kluwer Academic Publishers, pp. 439-459, (1989), hemoperfusion nevertheless requires systemic anticoagulation and also depletes coagulation factors and platelets from the blood. Moreover, the relatively large sorbent granules used in hemoperfusion columns have limited surface area (about 1000-10,000 m^2). Consequently, the available sorbent surface area is saturated within a few hours, clearance of bound chemicals rapidly diminishes, and a new column must be used.

[0006] Furthermore, clinical benefits of charcoal hemoperfusion may be offset by deleterious effects of bio-incompatibility. In one instance, a controlled study of patients with fulminant hepatic failure, all treated with aggressive intensive care including intracerebral pressure monitoring, demonstrated that patients treated by hemoperfusion had a generally lower survival rates than those treated with aggressive intensive care alone. The only exception was noted in patients having fulminant hepatic failure due to hepatitis A or B, for whom there was reported a "trend toward improved survival" when treated with charcoal perfusion. O'Grady, J.G. et al., Controlled Trials of Charcoal Hemoperfusion and Prognostic Factors in Fulminant Hepatic Failure, Gastroenterology, Vol. 94, pp. 1186-92 (1988).

[0007] As mentioned, standard hemodialysis (i.e. dialysis of blood against only a dialysate solution) has also been studied as a possible treatment for hepatic failure. However, benefits of hemodialysis may be similarly obscured by removal of substances (e.g. urea) known not to be toxins of hepatic failure. Additionally, hemodialysis requires the use of large volumes of dialysate solution which limits the mobility and increases the complexity of the machines, or alternatively, it requires the provision of a sorbent column to "regenerate" the dialysate.

[0008] In light of this extensive background, there remain needs for improved devices and methods for the extracorporeal treatment of blood or of blood fractions to effectively remove toxins, including both soluble and protein-bound toxins. The present invention addresses these needs.

SUMMARY OF THE INVENTION

[0009] According to the present invention there is provided a blood treatment instrument defining a blood circuit separated from a sorbent suspension at a first location by compliant membranes and separated from a sorbent suspension at a second location by hollow fiber membranes, said instrument comprising:

a plate dialyzer (PPD) defining a first blood side separated from a first sorbent suspension side by one or more

compliant membranes; said first blood side in fluid communication with a blood source line and a blood return line; said compliant membranes being formed to expand and compress in response to alternating negative pressure and positive pressure on said first sorbent suspension side of said dialyzer;
a sorbent suspension circulating means in fluid communication with said first sorbent side for circulating sorbent suspension through said first sorbent suspension side;
said sorbent suspension circulating means including an accumulator reservoir positioned between said first sorbent suspension side and a one way valve, whereby said accumulator reservoir is operable to alternately accumulate and expel sorbent suspension to apply alternating negative pressure and positive pressure on said first sorbent suspension side of said dialyzer and to thereby communicate said alternating negative pressure and positive pressure to said first blood side by causing expansion and contraction of said compliant membranes;
means for clamping said blood return line during application of negative pressure by said accumulator reservoir to thereby allow aspiration of blood into said first blood side through said blood source line;
means for clamping said blood source line during application of positive pressure by said accumulator reservoir to thereby cause blood to flow from said first blood side through said blood return line; characterised by a hollow fiber membrane device (HFD) defining a second blood side in fluid communication with said first blood side and separated from a second sorbent suspension side by one or more hollow fiber membranes; said hollow fiber membranes defining pores formed to pass middle molecular weight and/or protein bound blood toxins in response to alternating negative and positive pressure gradients across the hollow fiber membranes;

wherein said instrument is effective to circulate blood through said first blood side of said dialyzer, and through said second blood side of said hollow fiber device in a direction generally from said blood source line to said blood return line, by opening and closing of said blood source line clamping means and said blood return line clamping means, coupled with expansion and contraction of said compliant membranes caused by alternating negative and positive pressure on said first sorbent suspension side of said dialyzer; and

wherein alternating negative and positive pressures communicated to said blood circuit across said compliant membranes are effective to provide alternating pressure gradients across said hollow fiber membranes, thereby causing a blood fraction containing said middle molecular weight and/or protein bound blood toxins to alternately exit and re-enter the interior of said hollow fiber membranes, so as to contact a sorbent suspension in said second sorbent side, and effectuate removal of said toxins from said fluid and delivery of said toxins into said sorbent suspension.

[0010] The device is highly effective for removing protein-bound or middle molecular weight toxins from fluids such as blood, blood plasma or blood filtrate. In use, the device of the present invention provides a unique filtration process (e.g. a hemofiltration or plasmafiltration process) which includes the steps of passing a fluid, such as blood, containing protein-bound or middle molecular weight blood toxins, through the interior of a hollow fiber membrane, and during the passage of blood, circulating a sorbent suspension against exterior surfaces of the hollow fiber membrane. As a further step, during the passage of blood and circulation of sorbent suspension, the plasma fraction of the blood is caused to alternately exit and re-enter the interior of the membrane. Thereby, blood plasma contacts the sorbent suspension upon exit from the interior of the membrane, so as to effectuate removal of the toxins from the blood. This process is applied with preference to whole blood; however, the process is not so limited, as it will be applicable as well to the treatment of other fluids containing middle molecular weight and/or protein bound blood toxins, e.g. blood fractions such as isolated blood plasma or other blood toxin-containing fluids such as blood filtrate.

[0011] The preferred device of the invention includes a hollow fiber membrane, and a pump fluidly connected to the interior of the hollow fiber membrane and adapted to pass blood (or another fluid containing the toxins) through the interior. The device further includes a chamber surrounding the hollow fiber membrane, the chamber also being fluidly connected to a supply of sorbent suspension containing solid particulate adsorbent. A pump is adapted to circulate the sorbent suspension through the chamber and against exterior surfaces of the hollow fiber membrane. Means for causing the blood or other fluid or a fraction thereof passing through the interior of the membrane to alternately exit and re-enter the interior of the hollow fiber membrane are also provided.

[0012] The invention thus provides a device by which greater removal of protein-bound and middle molecular weight blood toxins from blood, blood plasma or blood filtrate can be achieved, and whereby efficient circulation of sorbents on the sorbent side of a variety of different types of extracorporeal treatment devices is effectuated. Additional objects, features and advantages of the present invention will be apparent from the description which follows.

BRIEF DESCRIPTION OF THE FIGURES

[0013]

Figure 1 is a perspective view of a preferred pressure/vacuum operated dialysis system which can be used in the invention.

Figure 2 is a schematic representation of the hydraulic system of the dialysis system of Figure 1.

Figure 3 is a schematic representation of the mechanics of operation of the preferred direct pressure/vacuum operated dialysis system of Figure 1 during the first part of blood inflow (Fig. 3A) and during the remainder of blood inflow and blood outflow (Fig. 3B).

Figure 4 is a schematic representation of the hydraulic circuit of a combined device incorporating the system of Figure 1 in series with a hollow fiber plasmafilter.

Figure 5(a) shows the blood-side pressure curve between the system of Figure 1 and the plasmafilter in the combined device of Figure 4, during several inflow-outflow cycles.

Figure 5(b) shows the sorbent-side pressure curve within the plasmafilter membrane package of the combined device of Figure 4. Mean blood-sorbent pressure difference is approximately zero.

Figure 6(a) shows a Langmuir isotherm for binding of bromsulphthalein (BSP) from saline (top line) and from porcine plasma (bottom line) to which it was first bound to charcoal.

Figure 6(b) shows a Langmuir isotherm for binding of unconjugated bilirubin from porcine plasma to which it was first bound to charcoal.

DESCRIPTION OF THE PREFERRED EMBODIMENT

[0014] For the purposes of promoting an understanding of the principles of the invention, reference will now be made to certain embodiments and specific language will be used to describe the same.

[0015] As indicated above, one preferred embodiment of this invention relates to an instrument which can be used for extracorporeal treatment of blood or a blood fraction by filtration, e.g. plasmafiltration (wherein plasma is filtered across a membrane) or hemofiltration (wherein middle molecular weight molecules (i.e. having molecular weights of about 300 to about 10,000) are filtered across a membrane), in a manner which provides the safe, consistent and effective removal of toxins, including protein-bound blood toxins and middle molecular weight blood toxins. This filtration can be used alone, or in connection with dialysis of the blood or blood fraction, for example using dialysis devices as described in US-A-5 277 820.

[0016] Likewise, the advantageous sorbent circulation system described in this prior application is effective to advance sorbent suspension through hollow fiber plasmafilters and hemofilters, and is generally applicable to advance sorbent suspension through a variety of extracorporeal treatment devices having blood and sorbent sides separated by a membrane, and thus also forms a part of tile applicant's invention.

[0017] The sorbent suspension used in the invention can include powdered surface adsorptive agents, physiologic electrolytes and macromolecular flow inducing agents. In general, these components are present in effective amounts to achieve the desired removal of substances from and electrolyte balance in the blood of the patient while maintaining the stability and fluidity of the sorbent suspension. Because plasmafiltration membranes as used in the invention can potentially pass endotoxins, it is preferred that the sorbent suspension be free from measurable endotoxins. While general sorbent suspension production techniques have been sufficient for these purposes, if necessary, measures can be taken sanitize or sterilize the suspension, for example using heat or radiation (e.g. gamma-radiation), to assure that the sorbent suspension is substantially free from bacteria or other microbial growth which could potentially generate endotoxins or other harmful substances.

[0018] The powdered surface adsorptive agent can be any one of many known to those practiced in this area, but is preferably powdered activated charcoal. Further, the powdered surface adsorptive agent preferably has an average particle diameter of not greater than about 100 microns. More preferably, this average particle diameter is less than about 50 microns, with 90% or more of the particles having diameters not greater than about 75 microns. Particles exceeding 75 microns in diameter can be screened if necessary. As one example, a suitable finely powdered activated charcoal is available from American Norit Company, Inc. of Jacksonville, Florida, U.S.A., which can be screened to remove particles larger than those desired.

[0019] The macromolecular flow inducing agents function to maintain the stability of the sorbent suspension formulation (i.e. helps to prevent solids from settling out of suspension) and maintain the flow properties of the suspension. One desirable flow inducing agent is a nonionic, hydroxyl-containing polymer such as a glycol derivative. Suitable agents of this type are available from BASF Wyandotte of Parsippany, New Jersey, U.S.A. under the trademark "Pluronic" polyols. These Pluronic polyols are polyoxyalkylene derivatives of propylene glycol. To date, applicant has used Pluronic F68, which functions both as a flow inducing agent and a defoaming agent. Another flow agent that has been

included in preferred suspensions is macroreticular polyvinylpyrrolidone.

[0020] The types and amounts of electrolytes included in the suspension formulation will depend upon the specific needs of the patient and will be readily determinable by physicians or others skilled in the area. Typically, the electrolytes will include sodium and chloride (e.g. optionally provided as sodium chloride), and can also include bicarbonate, potassium, calcium, or any other electrolytes to be regulated in the patient. As indicated, however, the types and amounts of electrolytes may vary widely depending on patient needs.

[0021] The sorbent suspension formulation may also include an ion-exchanger to bind ionic chemicals, e.g. ammonium, etc., which may occur in the patient's blood. Many suitable ion exchangers including both resins and other materials such as zeolites are known in the art. When included, the ion-exchanger is preferably a cation-exchange resin, which is desirably loaded with sodium or calcium. For example, to date, sodium polystyrene sulfonate has been a preferred material.

[0022] The surface adsorptive agent, electrolytes, flow inducing agents and any other additives will usually comprise about 5% to 30% by weight of the sorbent suspension formulation as a whole, with the remainder being water. Typically, solid sorbents will comprise about 2% to 25% by weight of the suspension formulation, and electrolytes will comprise 1% to 5% of the suspension formulation. Within these parameters, more preferred sorbent suspension formulations comprise about 2% to 20% powdered surface adsorptive agent, up to about 10% ion-exchanger, and up to about 1% flow agent such as a polyol and/or polyvinylpyrrolidone.

[0023] The sorbent suspension can also include viable hepatic cells, e.g. xenogenic or allogenic cells, alone or in combination with one or more of the solid adsorbents and other materials described above, to assist in the effective removal of toxins. For example, hepatocytes can be isolated from suitable donor tissue, purified and microencapsulated in polymer as described by Dixit et al., Hepatology 1990: 12: 1342. These microencapsulated cells can then be used directly in the sorbent suspension, or can be cryopreserved until use, for example as described by Dixit et al., Transplantation 1993; 55: 616-22. When hepatic cells are so used, plasma is effectively separated from the blood by passage through the plasmafilter membrane, and proteins and toxins are convected into contact with the cells circulating exterior of the membrane. After the cells have acted upon the toxins, the plasma is returned through the membrane and back into the patient.

[0024] In connection with plasmafiltration or hemofiltration devices and methods, there are many suitable hollow fiber membranes which are known for use in plasmafiltration or hemofiltration of blood, and those skilled in the area will 1 be readily able to select and utilize a suitable membranes in the present invention. Such membranes can be, for example, cellulosic membranes (e.g. cellulose acetates), and will have pore sizes sufficiently large to allow passage of plasma proteins (e.g. in plasmafiltration) and/or middle molecular weight blood toxins (e.g. in hemofiltration), suitably having molecular weight cutoffs of 50,000 or above, e.g. 50,000 to 6,000,000. Suitable plasmafiltration and hemofiltration membranes include, for example, those known under the designations F-80 (50',000 m.w. cutoff, Fresenius USA, Inc., Walnut Creek, CA), Altrex 140 (70,000 m.w. cutoff, Althin Medical, Inc., Miami Lakes, FL)), CT190G (60,000 m.w. cutoff, Baxter, Deerfield, IL), and Plasmaflo AP-05H(L) (1,000,000 m.w. cutoff, Asahi Medical Co., Ltd., Tokyo, Japan). More preferred plasmafiltration or hemofiltration membranes will have pore sizes which transmit albumin or middle molecular weight molecules with selectivity over larger molecules, and thus will provide removal of toxins while minimizing potential interference with other blood functions. For example, the Plasmaflow AP-05H(L) plasma separator (0.5 square meters) has about a 5% rejection of albumin during unidirectional filtration, but about an 80% rejection of macroglobulins.

[0025] In connection with dialysis, there are many dialyzer membranes which are known for use in dialyzing body fluids such as blood, and those skilled in the area will be readily able to select and utilize a suitable membranes in the present invention. One suitable membrane is a cellulosic membrane, particularly one composed of regenerated cuproammonium cellulose (Cuprophan)®.

[0026] In circumstances where only plasmafiltration or hemofiltration (and not dialysis) of the blood or other fluid is desired, the membrane in the dialysis instrument need not be a dialysis membrane, and thus may be one which is impermeable to blood and its components, e.g. a membrane formed from a suitable compliant plastic film. Moreover, where only plasmafiltration or hemofiltration is desired, the dialysis instrument need not be employed at all, and any means of circulating the sorbent suspension against the exterior of the hollow fiber membranes while passing the blood or other fluid through the interior of the membranes (with bidirectional flow of the blood or fluid across the membranes) will be suitable. For example, the hollow fiber membrane cartridge could have sorbent side connections to a container filled with sorbent suspension. While the sorbent suspension is circulated through the cartridge, for example by a roller pump, the pressure changes in the blood side (created automatically by roller pumps) would create the desired bidirectional flow of plasma or other fluid across the membranes. Such systems will provide high clearance of protein-bound or middle molecular weight toxins with great simplicity and low cost.

[0027] The plasmafiltration or hemofiltration methods are performed in connection with a dialysis instrument including a parallel plate dialyzer and moving the sorbent suspension formulation in a counter-current mode by the direct application of alternating negative pressure and positive pressure on the dialysate side, as described in more detail in

Examples 1 and 2 below. The preferred system also creates a slight back and forth motion of the sorbent suspension formulation, which agitates, locally mixes, and helps to prevent settling of the suspension.

[0028] Extracorporeal blood-treatments effected using the instrument of the invention can be used to safely and effectively treat the coma and illness of hepatic failure and to improve a patient's clinical condition as evidenced by improved physiologic and neurologic patient status. The instrument of this invention can also be successfully used in treating drug overdose, even with highly-protein-bound drugs (i.e. drugs which are 75% or more protein bound). It is also expected that the instrument of the invention will be effective in treating patients with renal failure, uremia, or other conditions benefited by removal of toxins from the blood. Further, plasmafiltration and/or dialysis methods effected by the instrument of the invention can be used in hemofiltration to treat and remove toxins from the hemofiltration ultrafiltrate, and return the treated ultrafiltrate to blood. In this manner, the use of large volumes of sterile replacement fluid can be ameliorated or eliminated.

[0029] The invention will now be described with reference to the following specific Examples which are illustrative, and not limiting, of the invention.

EXAMPLE 1

Operation and Components of Preferred Vacuum/Pressure Operated Flow-Through Dialysis System

[0030] Figure 1 is a perspective view of a preferred dialysis system sitting on a standard hospital cart, which can be used in methods of the invention. Generally, the preferred dialysis system is similar in some respects to the dialysis instrument disclosed in my earlier U.S. Patent No. 4,661,246 issued April 28, 1987,

However, to fill and empty the dialyzer of blood, the present system uses the direct application of pressure and vacuum to give positive and negative pressure changes in the dialysate. This increases the blood flow and enhances the mixing of the sorbent suspension formulation, as well as helps to maintain optimal chemical gradients across the dialysis membrane.

[0031] with continued reference to Figure 1, the dialysis system includes a machine base 12, reservoir tank 13 with cover 14, a sorbent bag 15 containing sorbent suspension materials, disposable pack 16 (including the plate dialyzer), and power supply 17 (providing vacuum, pressure, and DC power to the machine base). Referring now also to Figures 2 and 3, Figure 2 is a hydraulic schematic of the dialysis system, and Figure 3 provides in parts A and B a summary of the mechanics and hydraulics of operation of the system during blood inflow and outflow, respectively. Generally, in the following discussion, the numbers 20-47 will be used to designate components on the disposable pack 16, whereas numbers 50 and above will designate components of the machine base 12. In Figure 1, the machine base 12 and disposable pack 16 are shown separated. Of course, in use together, the pack 16 is mounted to machine base 12 and their respective components assembled generally as follows.

[0032] Vacuum/pressure line 20 from top port 21 of accumulator 22 is connected to vacuum pressure port 50 on machine base 12 which feeds vacuum and pressure from the respective sources thereof in power supply 17. Prime tube 23 is seated into the upper side of prime/rinse clamp 51 and through prime fluid sensor 52. The blood inflow tube 24 is seated into the lower side of prime rinse clamp 51, blood inflow clamp 53 and the blood inflow sensor 54. The blood outflow tube 25 is seated into blood outflow clamp 55 and blood outflow sensor 56, and fluid level sensor 57 is placed onto accumulator 22. Reinfusate tube 26 is loaded into reinfusate pump 58 and reinfusate fluid sensor 59. Dialysate tube 27 (prior to the "Y" split) is loaded into dialysate pump 60 and its end connected to water port 61. Branch of dialysate tube 28 (after the "Y" split) which connects to the dialysate inlet 29 of dialyzer 30 is seated into dialysate-in clamp 62. Filtrate line 31 is loaded into filtrate pump 63 and into filtrate fluid sensor 64. Filtrate line 31 is also connected to filtrate disposal bag 32 which is vented. Three liters of sterile water are added to reservoir tank 13. Sorbent bag 15 is suspended from reservoir cover 14. Tubes 33 (leading to dialysate inlet 29) and 34 (leading to the exit port of accumulator 22 and also connected to dialysate outlet 35 via line 36) are connected to lines 37 and 38 provided on and leading into sorbent bag 15.

[0033] The following steps are conducted under sterile conditions. Blood inflow line 24 and blood outflow line 25 are connected to blood inlet 39 and blood outlet 40 of dialyzer 30, respectively. Reinfusate solution (e.g. $CaCl_2$ solution and appropriate amounts of KCl and/or NaCl solution) is injected into reinfusate bag 41. Reinfusate line 26 is connected to reinfusate bag 41 and a drip chamber in the line is partially filled. Prime tube 23 is connected to prime bottle 42 containing priming fluid, e.g. 5% dextrose. If desired, replacement fluid can be provided via fluid replacement line 43.

[0034] Thus, after the above assembly, the blood inflow 24 and blood outflow 25 tubes pass from a single access line 44 through clamps 53 and 55 and optical monitors 54 and 56 to connect to the top 39 and bottom 40 openings of the blood side of the dialyzer 30. Cylindrical accumulator 22 attaches to the dialysate space at the top opening 35 of the dialysate side of dialyzer 30, and alternating strong vacuum (i.e. negative pressure) and modest positive pressure in accumulator 22 (provided by line 20 through port 21 above the fluid level) alternately draws dialysate into and expels dialysate from accumulator 22, which expands and compresses the membranes of dialyzer 30 (as illustrate by the

arrows, Fig. 3), while the automatically controlled blood inflow and outflow clamps 53 and 55 assure that blood passes unidirectionally through the dialyzer 30, at an average rate of up to 250 ml/min (in 5 cycles). The ratio of inflow/outflow cycle times determines the ultrafiltration rate, from a minimum of about 200 ml/hr at a ratio of about 1.45, to about 600 ml/hr at a ratio of 2.45.

[0035] In the preferred dialysis system utilized in the specific Examples, the dialyzer was a 1.6m^2 COBE parallel screen-plate dialyzer having dialysis membranes composed of regenerated cuproammonium cellulose (Cuprophan)® and having a functional molecular weight cut-off of about 3000 daltons, i.e. only molecules of about 3000 daltons or less will pass through the membrane.

[0036] As opposed to many previously-known dialysis systems, the system used in the invention contains a sorbent suspension in the dialysate instead of merely a dialysis solution. Flow of the suspension is generally counter-current, and is both bidirectional between the accumulator 22 and dialyzer 30, and circular between the dialyzer 30 and sorbent reservoir 15.

[0037] In summary, during the first part of blood inflow (see particularly Fig. 3A), clamp 62 on the dialysate inflow line 33 opens, allowing sorbent suspension to flow from the sorbent reservoir 15 through the entire dialyzer 30, filling the accumulator 2 to the level of sensor 57. Clamp 62 then closes and remains closed during the remainder of inflow and all of outflow (see particularly Fig. 3B), when pressure in the accumulator 22 returns some suspension to the dialyzer 30 and passes some through one-way valve 45 to return to the reservoir 15 via dialysate return line 34. In typical operation, each minute, about 900 ml of sorbent suspension flows into accumulator 22 (in 5 cycles). 600 ml of sorbent suspension flows back into the dialyzer 30, and 300 ml flows from the accumulator 22 into the sorbent reservoir 15. This, along with the expansion and contraction of the dialyzer membranes, keeps the sorbent suspension well mixed at the dialyzer membrane surface. As can be seen, both the blood side and dialysate side pressures alternate between positive and negative pressure, while the spring action of the plate dialyzer membranes ensures that there is constantly a positive pressure gradient from blood side to dialysate side.

[0038] In one suitable system, sorbent bag 15 initially contains dry sorbent materials to which the system automatically adds 1.5 liters of sterile water from reservoir tank 13 via port 61 during priming. This operation is powered by dialysate pump 60. For the Examples given below, the sorbent materials in bag 15 were as follows:

- 140 grams powdered activated charcoal (300,000 square meters surface area, between 5 and 53 micron mean particle diameter, 70 micron maximum particle diameter)
- 80 grams cation exchanger (sodium polystyrene sulfonate, PSS, functional binding of 80 mEq).
- 1.5 grams Pluronic F68®.
- 3.0 grams polyvinylpyrrolidone (PVP).
- sodium bicarbonate and sodium chloride to result in physiologic starling concentrations in the dialysate sorbent suspension after priming (sodium-140 mEq/L, bicarbonate-35 mEq/L, chloride-105 mEq/L).

[0039] The priming fluid for the blood side of the dialysis system was one liter of 5% dextrose from container 42 attached to blood inflow tube 24 via tube 23. During priming, priming/rinse clamp automatically opens prime tube 23 while closing blood inflow tube 24. Priming fluid is thus pulled into the system rather than blood. Glucose passes across the membranes of the dialyzer 30, and 20 grams binds to the charcoal, while sodium chloride, and bicarbonate pass from the suspension into the priming fluid. During dialysis, glucose disassociates from the charcoal and returns to the patient (unless the patient's glucose is very high). A reinfusate of sterile calcium chloride and potassium chloride was pumped by reinfusate pump 58 from reinfusate container 41 through tube 26 into the outflow line 25 at a diminishing rate throughout the treatment, to offset removal by the cation exchanger.

[0040] The system also includes a variety of sensors to make operation safe, simple and highly automated, including:

- a scale to weigh the entire top of the machine, to measure volumes ultrafillered from and returned to the patient;
- blood sensors (54 and 56) to measure foam, bubbles, particles of blood in the inflow and outflow lines 24 and 25, and to measure flow rate on the inflow line 24;
- hemoglobin sensor 46 to chemically detect hemoglobin within the sorbent suspension if there is a membrane blood leak. For this function, a filtrate collector 47 provides a solid-free sample of the dialysate fluid to hemoglobin sensor tape which changes color if hemoglobin is present. The tape is automatically wetted with samples of dialysate, advanced and monitored for color change by a reflectometer. The wetting of the tape is controlled by filtrate pump

63 which further pumps excess filtrate via tube 31 into collection container 32.

- empty line sensors on all fluid-filled lines;
- temperature sensor for fluid in the reservoir tank 13 surrounding the sorbent bag 15 (optimally heated to about 37° to 40°C by heating elements also provided in the machine).

[0041] The computers of the system automate many of the steps of treatment, including:

- priming of the machine, observing lines to determine that all air is removed;
- returning fluid to the patient when desired final weight is obtained or on command (for the latter, automatically adjusting ultrafiltration to reach desired final weight).
- rinsing the dialyzer and blood lines at the end of treatment; and
- recording, storing and transferring data concerning progress of each treatment.

EXAMPLE 2

COMBINED DIALYSIS/PLASMAFILTER or HEMOFILTER DEVICE

[0042] Figure 4 provides a schematic diagram showing the hydraulics of a combined dialysis/plasmafilter device in accordance with the invention. As shown, the device incorporates a parallel plate dialyzer ("PPD") connected in series with a hollow fiber membrane device ("HFD"). The HFD can be incorporated in any suitable location within the sorbent circulation side of the PPD.
Preferably, the HFD will be incorporated to as to achieve high bidirectional plasma flow across the membranes of the HFD, with a net flow of about zero to prevent increasing sorbent volume (which would increase the volume of distribution for albumin and increase loss of albumin from the patient). The HFD is also desirably incorporated so as to provide blood treatment rates over 150 ml/min., to allow high filtration rates across the membranes and permit high clearance of protein-bound or middle molecular weight substances.
[0043] In the illustrated arrangement, the HFD is connected in series with the PPD such that sorbent suspension exiting the sorbent reservior first passes through the PPD and then the HFD. More particularly, sorbent is first drawn from sorbent bag 101 and into sorbent inlet 102 of the PPD. Sorbent exits sorbent outlet 103 and is drawn into accumulator reservior 104, whereafter it is expelled from accumulator reservior 104 and passes through check valve 105. The sorbent suspension then passes into HFD inlet 106 and through the outer chamber of the HFD, thus passing into contact with exterior surfaces of the hollow fibers 107 in the HFD package. Sorbent suspension exits the HFD from outlet 108, and passes through blood leak detector 109 and back into sorbent bag 101. The PPU can be suitably operated as described in Example 1 above. In this manner, the sorbent suspension is also effectively agitated and mixed at the surface of the membranes in the HFD. Additionally, when alternating positive and negative pressure is applied to the sorbent circuit via the accumulator reservior 104, check valve 105 prevents negative pressure from being applied to the HFD sorbent side, and creates only intermittent positive pressure (Figure 5(b)). In this system, the blood-side (see Figure 5(a)) and dialysate-side pressures vary with each cycle, but are balanced on average, thus creating a bidirectional flow in each cycle but with zero net filtration (there is net sorbent to blood filtration in the HFD, offsetting ultrafiltration of the PPD, several hundred ml/hr.).
[0044] On the blood side, blood passes from the patient access and into blood inlet 110 of the PPD, with the intermediate addition of saline from reservior 111. Where a dialysis membrane (as opposed to an impermeable membrane) is installed in the PPD, the blood is dialyzed in the PPD as described above. Blood then exits the PPD through outlet 112 and passes into interior channels of the hollow fibers of the HFD (commercial HFD devices have a package including a plurality of hollow fiber membranes). At this point, the alternating positive and negative pressure applied on the sorbent side causes a bidirectional flow of plasma across the hollow fiber membranes, that is, the blood plasma exits and then re-enters the hollow fiber membranes. While exterior of the hemofilter or plasmafilter membranes, middle molecular weight toxins and/or plasma proteins, including proteins to which toxic substances are bound, come into contact with the sorbent suspension. The toxic substances are adsorbed to the adsorbents, and in the case of plasmafiltration, the proteins, now free of toxins, are passed back into the hollow fiber membranes. Thus, effective plasmafiltration or hemofiltration of the blood is achieved as the blood passes through the HFD. Blood exits the HFD via outlet 113, and is returned to the patient through the patient access.
[0045] The pressures of the blood-side and sorbent-side will vary with the particular HFD devices employed. Thus,

with a particular HFD device, in vitro tests can be done to measure filtration rate, and the vacuum and pressure operating the system will be adjusted to attain zero net filtration. Moreover, to optimize blood flow, adjustments to the ratio of inflow/outflow times can be made. The combined PPD/HFD system will, like the system described in Example 1, measure the rate of ultrafiltration by weighing the entire top of the device, including the sorbent bag. But, since the goal is net ultrafiltration of about zero, there is no need for the long inflow times of the system of Example 1. Better blood flow will be obtained using approximately equal inflow and outflow times. During in vitro tests, for example with pig blood, the driving pressures can be adjusted as above, and the net blood flow determined (by change of weight of the 3 liter container during each cycle). The inflow-outflow times can then be adjusted to give maximum blood flow. Preferably, the 200-225 ml/min average blood flow of the system of Example 1 is maintained.

EXAMPLE 3

BLOOD TREATMENT WITH DIALYSIS/PLASMAFILTER OR HEMOFILTER DEVICE

[0046] Charcoal has the capacity to very effectively adsorb middle molecular weight molecules and protein-bound toxins (see, e.g., Pigs. 6(a) and 6(b) which provide Langmuir isotherms of the adsorption of BSP from plasma and saline and of bilirubin from plasma). In the following studies, the PPD/HFD device described in Example 2 was used to determine clearance rates of some protein-bound and middle molecular weight substances from blood. 3 liters of fresh pig blood were spiked with various substances (Shown in Table 1 below), and the blood was treated using the PPD/HFD device. During several hours of treatment, the blood was continuously infused with the substances at a rate designed to maintain a constant concentration (calculated by the predicted clearance of the system). The clearances were then determined by dividing the rate of infusion by the steady-state concentration of the substance. If the blood volume changed, then the change was included in the calculation of clearance. The results are shown in Table 1, in which "Creat" - creatinine, "Bili" - bilirubin, BSP, and "Vanco®" - vancomycin. Among these, creatinine is a small, non-protein bound substance, bilirubin, Elavil® and BSP are small, highly protein-bound molecules, and vancomycin is a middle molecular weight, non-protein bound substance.

TABLE 1

BLOOD FLOW AND CLEARANCES (ml/min)						
Membrane	Ave Ob.	Creat	Bili	BSP	Elavil®	Vanco®
PPD only	200	140	0	0	12	0
F-80	150	130	12	n/a	40	-
Altrex® 140 (70K)	180	130	5	n/a	-	-
Althin*	140	90	5	n/a	19	37
CT190G	160	85	0	-	-	G2
Plasmaflo® AP-05H(L)	140	95	43	n/a	n/a	35

- (dash) = no data
n/a = data not currently available
* developmental filter from Althin Medical, Inc., m.w. cutoff = 100,000.

[0047] As can be seen, use of the HFD can provide significant increases in the clearance of middle molecular weight and protein-bound substances, and can be used in connection with the PPD to provide effective overall clearance of small and larger substances, both protein-bound and non-protein-bound.

Claims

1. A blood treatment instrument defining a blood circuit separated from a sorbent suspension at a first location by compliant membranes and separated from a sorbent suspension at a second location by hollow fiber membranes, said instrument comprising:

   a plate dialyzer (PPD) defining a first blood side separated from a first sorbent suspension side by one or more compliant membranes; said first blood side in fluid communication with a blood source line and a blood return line; said compliant membranes being formed to expand and compress in response to alternating negative pressure and positive pressure on said first sorbent suspension side of said dialyzer;
   a sorbent suspension circulating means in fluid communication with said first sorbent side for circulating sorb-

ent suspension through said first sorbent suspension side;
said sorbent suspension circulating means including an accumulator reservoir (104) positioned between said first sorbent suspension side and a one way valve (105), whereby said accumulator reservoir (104) is operable to alternately accumulate and expel sorbent suspension to apply alternating negative pressure and positive pressure on said first sorbent suspension side of said dialyzer and to thereby communicate said alternating negative pressure and positive pressure to said first blood side by causing expansion and contraction of said compliant membranes;
means for clamping said blood return line during application of negative pressure by said accumulator reservoir (104) to thereby allow aspiration of blood into said first blood side through said blood source line;
means for clamping said blood source line during application of positive pressure by said accumulator reservoir (104) to thereby cause blood to flow from said first blood side through said blood return line;

characterised by a hollow fiber membrane device (HFD) defining a second blood side in fluid communication with said first blood side and separated from a second sorbent suspension side by one or more hollow fiber membranes; said hollow fiber membranes defining pores formed to pass middle molecular weight and/or protein bound blood toxins in response to alternating negative and positive pressure gradients across the hollow fiber membranes;

wherein said instrument is effective to circulate blood through said first blood side of said dialyzer, and through said second blood side of said hollow fiber device in a direction generally from said blood source line to said blood return line, by opening and closing of said blood source line clamping means and said blood return line clamping means, coupled with expansion and contraction of said compliant membranes caused by alternating negative and positive pressure on said first sorbent suspension side of said dialyzer; and

wherein alternating negative and positive pressures communicated to said blood circuit across said compliant membranes are effective to provide alternating pressure gradients across said hollow fiber membranes, thereby causing a blood fraction containing said middle molecular weight and/or protein bound blood toxins to alternately exit and re-enter the interior of said hollow fiber membranes, so as to contact a sorbent suspension in said second sorbent side, and effectuate removal of said toxins from said fluid and delivery of said toxins into said sorbent suspension.

2. The blood treatment instrument of claim 1 wherein a sorbent suspension storage reservoir (101) is in fluid communication with said first sorbent suspension side;

wherein said first sorbent suspension side is located between said sorbent suspension storage reservoir (101) and said accumulator reservoir (104); and

wherein said accumulator reservoir (104) is located between said first sorbent suspension side and said one way valve (105) so that sorbent suspension accumulated in said accumulator reservoir (104) under negative pressure passes from said sorbent suspension storage reservoir (101) through said first sorbent suspension side, and so that sorbent suspension expelled from said accumulator reservoir (104) passes partially into said first sorbent suspension side of said dialyzer and partially through said one way valve (105).

3. The blood treatment instrument of claim 1 which is adapted to cause counter-current flow of said sorbent suspension and said blood.

4. The blood treatment instrument of claim 1, wherein said hollow fiber membrane is a hemofiltration membrane.

5. The blood treatment instrument of claim 1, wherein said hollow fiber membrane is a plasmafiltration membrane.

6. The blood treatment instrument of claim 1, wherein said hollow fiber membrane defines pores having molecular weight cutoffs of at least 50,000 daltons.

7. The blood treatment instrument of claim 1, wherein said hollow fiber membrane defines pores having molecular weight cutoffs of from 50,000 to 6,000,000 daltons.

8. The blood treatment instrument of claim 1, wherein said hollow fiber membrane transmits albumin with selectivity over larger proteins.

9. The blood treatment instrument of claim 1, wherein said compliant membrane has a molecular weight cut-off of 3000 daltons.

10. The blood treatment instrument of claim 1, wherein said compliant membrane is impermeable to blood and its

components.

Patentansprüche

1. Blutbehandlungsinstrument, das einen Blutkreislauf definiert, die von einer Sorptionsmittelsuspension an einer ersten Stelle durch Federungsmembrane getrennt ist und von einer Sorptionsmittelsuspension an einer zweiten Stelle durch Hohlfasermembrane getrennt ist, wobei das Instrument umfasst:

einen Plattendialysator (PPD), der eine erste Blutseite getrennt von einer ersten Sorptionsmittelsuspensionsseite durch ein oder mehrere Federungsmembrane definiert; wobei die erste Blutseite in einer Fluidkommunikation mit einer Blutquellenleitung und einer Blutrückführungsleitung ist; wobei die Federungsmembrane gebildet sind, um sich im Ansprechen auf einen wechselnden negativen Druck und positiven Druck auf der ersten Sorptionsmittelsuspensionsseite des Dialysators auszudehnen und zu komprimieren;

eine Sorptionsmittelsuspensions-Zirkulationseinrichtung in einer Fluidkommunikation mit der ersten Sorptionsmittelseite zum Zirkulieren einer Sorptionsmittelsuspension durch die erste Sorptionsmittelsuspensionsseite;

wobei die Sorptionsmittelsuspensions-Zirkulationseinrichtung einschließt: ein Sammelreservoir (104), das zwischen der ersten Sorptionsmittelsuspensionsseite und einem Einwegventil (105) positioniert ist, wobei das Sammelreservoir (104) betreibbar ist, um abwechselnd eine Sorptionsmittelsuspension zu sammeln und auszustoßen, um einen abwechselnden negativen Druck und positiven Druck auf die erste Sorptionsmittelsuspensionsseite des Dialysators anzuwenden und um dadurch den abwechselnden negativen Druck und positiven Druck an die erste Blutseite zu kommunizieren, indem eine Ausdehnung und Kontraktion der Federungsmembrane verursacht wird;

eine Einrichtung zum Klemmen der Blutrückführungsleitung während einer Anwendung eines negativen Drucks durch das Sammelreservoir (104), um dadurch eine Ansaugung von Blut in die erste Blutseite durch die Blutquellenleitung zu ermöglichen;

eine Einrichtung zum Klemmen der Blutquellenleitung während einer Anwendung eines positiven Drucks durch das Sammelreservoir (104), um dadurch zu bewirken, dass Blut von der ersten Blutseite durch die Blutrückführungsleitung fließt;

gekennzeichnet durch eine Hohlfasermembraneinrichtung (HFD), die eine zweite Blutseite in Fluidkommunikation mit der ersten Blutseite definiert und von einer zweiten Sorptionsmittelsuspensionsseite **durch** ein oder mehrere Hohlfasermembrane getrennt ist; wobei die Hohlfasermembrane Poren definieren, die gebildet sind, um Blutgiftstoffe mit einem mittleren molekularen Gewicht und/oder Protein-gebundene Blutgiftstoffe im Ansprechen auf abwechselnde negative und positive Durckgradienten über die Hohlfasermembrane zu führen;

wobei das Instrument effektiv ist, um Blut **durch** die erste Blutseite des Dialysators und **durch** die zweite Blutseite der Hohlfasereinrichtung in einer Richtung allgemein von der Blutquellenleitung zu der Blutrückführungsleitung zu zirkulieren, indem die Blutquellenleitungs-Klemmeinrichtung und die Blutrückführungsleitungs-Klemmeinrichtung, gekoppelt mit einer Ausdehnung und Kontraktion der Federungsmembrane, verursacht **durch** einen abwechselnden negativen und positiven Druck auf der ersten Sorptionsmittelsuspensionsseite des Dialysators, geöffnet und geschlossen werden;

wobei die abwechselnden negativen und positiven Drucke, die an dem Blutkreislauf über die Federungsmembrane kommuniziert werden, effektiv sind, um abwechselnde Druckgradienten über die Hohlfasermembrane bereitzustellen, wodurch bewegt wird, dass ein Blutteil, der die Blutgiftstoffe mit dem mittleren molekularen Gewicht und/oder Protein-gebundene Blutgiftstoffe enthält, abwechselnd aus dem Inneren der Hohlfasermembrane heraustritt und erneut in das Innere der Hohlfasermembrane eintritt, um so eine Sorptionsmittelsuspension in der zweiten Sorptionsmittelseite zu kontaktieren und eine Entfernung der Giftstoffe von dem Fluid und eine Lieferung der Giftstoffe in die Sorptionsmittelsuspension hinein zu bewirken.

2. Blutbehandlungsinstrument nach Anspruch 1, wobei ein Sorptionsmittelsuspension-Speicherungsreservoir (101) in einer Fluidkommunikation mit der ersten Sorptionsmittelsuspensionsseite ist;

wobei die erste Sorptionsmittelsuspensionsseite zwischen dem Sorptionsmittelsuspensions-Speicherungsreservoir (101) und dem Sammelreservoir (104) angeordnet ist;

wobei das Sammelreservoir (104) zwischen der ersten Sorptionsmittelsuspensionsseite und dem Einweg-

ventil (105) angeordnet ist, so dass die Sorptionsmittelsuspension, die in dem Sammelreservoir (104) unter dem negativen Druck gesammelt wird, von dem Sorptionsmittelsuspensions-Speicherungsreservoir (101) durch die erste Sorptionsmittelsuspensionsseite geht, und so, dass die Sorptionsmittelsuspension, die von dem Sammelreservoir (104) ausgestoßen wird, teilweise in die erste Sorptionsmittelsuspensionsseite des Dialysators und teilweise durch das Einwegventil (105) geht.

3. Blutbehandlungsinstrument nach Anspruch 1, welches dafür ausgelegt ist, um einen Gegenstromfluß der Sorptionsmittelsuspension und des Bluts zu verursachen.

4. Blutbehandlungsinstrument nach Anspruch 1, wobei die Hohlfasermembran eine Hämofiltrationsmembran ist.

5. Blutbehandlungsinstrument nach Anspruch 1, wobei die Hohlfasermembran eine Plasmafiltrationsmembran ist.

6. Blutbehandlungsinstrument nach Anspruch 1, wobei die Hohlfasermembran Poren definiert, die Begrenzungen des molekularen Gewichts von wenigstens 50000 Daltons aufweisen.

7. Blutbehandlungsinstrument nach Anspruch 1, wobei die Hohlfasermembran Poren definiert, die Begrenzungen des molekularen Gewichts von 50000 bis 6000000 Daltons aufweisen.

8. Blutbehandlungsinstrument nach Anspruch 1, wobei die Hohlfasermembran Albumin mit einer Selektivität gegenüber größeren Proteinen überträgt.

9. Blutbehandlungsinstrument nach Anspruch 1, wobei die Federungsmembran eine Begrenzung des molekularen Gewichts von 3000 Daltons aufweist.

10. Blutbehandlungsinstrument nach Anspruch 1, wobei die Federungsmembran nicht permeabel für Blut und dessen Komponenten ist.

Revendications

1. Instrument de traitement du sang définissant un circuit de sang séparé d'un sorbant en suspension au niveau d'un premier emplacement par des membranes souples et séparé d'un sorbant en suspension au niveau d'un deuxième emplacement par des membranes de fibres creuses, ledit instrument comprenant:

un dialyseur à plaque (PPD) définissant un premier côté du sang séparé d'un premier sorbant en suspension par une ou plusieurs membranes souples; ledit premier côté du sang étant en communication de fluide avec une ligne de source de sang et une ligne de retour du sang; lesdites membranes souples étant destinées à être dilatées et comprimées en réponse à l'application d'une pression négative et d'une pression position alternées audit premier côté du sorbant en suspension dudit dialyseur;

un moyen de circulation du sorbant en suspension, en communication de fluide avec ledit premier côté du sorbant pour faire circuler le sorbant en suspension à travers ledit premier côté du sorbant en suspension;

ledit moyen de circulation du sorbant en suspension englobant un réservoir accumulateur (104) positionné entre ledit premier côté du sorbant en suspension et une soupape d'arrêt (anti-reflux) (105), ledit réservoir accumulateur (104) pouvant ainsi être actionné pour accumuler et expulser alternativement le sorbant en suspension afin d'appliquer alternativement une pression négative et une pression positive audit premier côté du sorbant en suspension dudit dialyseur et communiquer ainsi ladite pression négative et ladite pression positives alternées audit premier côté du sang en entraînant une dilatation et une contraction desdites membranes souples;

un moyen pour serrer ladite ligne de retour du sang au cours de l'application d'une pression négative par ledit réservoir accumulateur (104), pour permettre ainsi l'aspiration du sang dans ledit premier côté du sang à travers ladite ligne de source du sang;

un moyen pour serrer ladite ligne de source du sang au cours de l'application d'une pression positive par ledit réservoir accumulateur (104) pour entraîner ainsi l'écoulement du sang dudit premier côté du sang à travers

ladite ligne de retour du sang;

caractérisé par un dispositif à membrane de fibres creuses (HFD) définissant un deuxième côté du sang, en communication de fluide avec ledit premier côté du sang et séparé d'un deuxième côté du sorbant en suspension par une ou plusieurs membranes de fibres creuses; lesdites membranes de fibres creuses définissent des pores formés de sorte à transférer des toxines du sang de poids moléculaire moyen et/ou à lien protéinique en réponse aux gradients alternés des pressions négative et positive, à travers les membranes de fibres creuses;

ledit instrument servant à faire circuler le sang à travers ledit premier côté du sang dudit dialyseur et à travers ledit deuxième coté du sang dudit dispositif de fibres creuses dans une direction allant en général de ladite ligne de source du sang vers ladite ligne de retour du sang, par ouverture et fermeture dudit moyen de serrage de la ligne de source du sang et dudit moyen de serrage de la ligne de retour du sang, combinées à une dilatation et une contraction desdites membranes souples, entraînées par l'application alternée d'une pression négative et d'une pression positive audit premier côté du sorbant en suspension dudit dialyseur; et

lesdites pressions négative et positive alternées communiquées audit circuit du sang par l'intermédiaire desdites membranes souples servant à établir des gradients de pression alternés à travers lesdites membranes de fibres creuses, entraînant ainsi alternativement la sortie d'une fraction du sang contenant lesdites toxines du sang à poids moléculaire moyen et/ou à lien protéinique de l'intérieur desdites membranes de fibres creuses et sa rentrée dans celles-ci, de sorte à contacter un sorbant en suspension dans ledit deuxième côté du sorbant et à entraîner l'élimination desdites toxines dudit fluide et le transfert desdites toxines dans ledit sorbant en suspension.

2. Instrument de traitement de sang selon la revendication 1, dans lequel un réservoir de stockage du sorbant en suspension (101) est en communication de fluide avec ledit premier côté du sorbant en suspension;

ledit premier côté du sorbant en suspension étant agencé entre ledit réservoir de stockage du sorbant en suspension (101) et ledit réservoir accumulateur (104); et

ledit réservoir accumulateur (104) étant agencé entre ledit premier côté du sorbant en suspension et ladite soupape d'arrêt (105), ledit sorbant en suspension accumulé dans ledit réservoir accumulateur (104) soumis à une pression négative passant dudit réservoir de stockage du sorbant en suspension (101) à travers ledit premier côté du sorbant en suspension, le sorbant en suspension expulsé dudit réservoir accumulateur (104) passant en partie dans ledit premier côté du sorbant en suspension dudit dialyseur et en partie à travers ladite soupape d'arrêt (105).

3. Instrument de traitement de sang selon la revendication 1, destiné à entraîner un écoulement à contre-courant dudit sorbant en suspension et dudit sang.

4. Instrument de traitement de sang selon la revendication 1, dans lequel ladite membrane de fibres creuses est une membrane d'hémofiltration.

5. Instrument de traitement de sang selon la revendication 1, dans lequel ladite membrane de fibres creuses est une membrane de plasmafiltration.

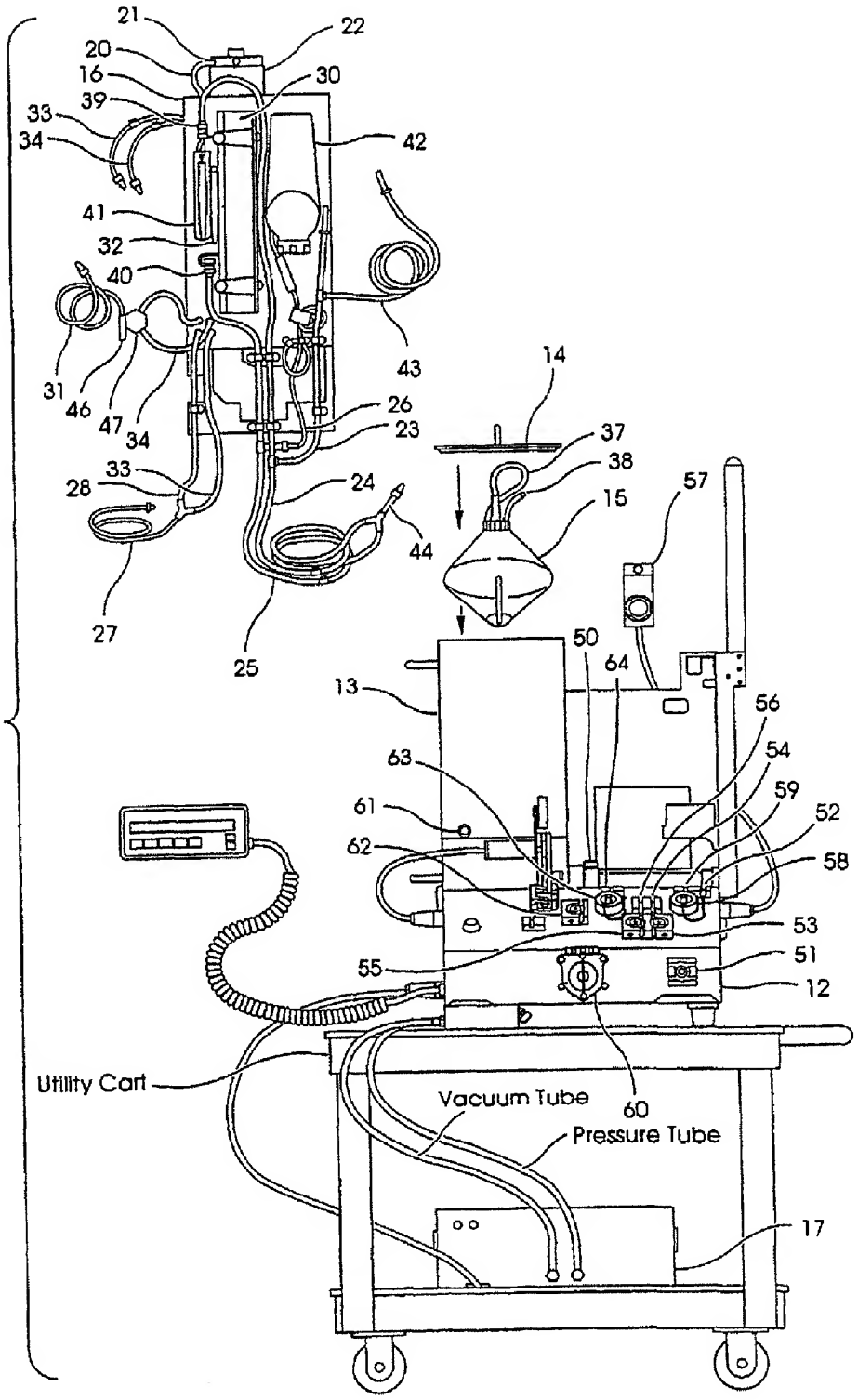
6. Instrument de traitement de sang selon la revendication 1, dans lequel ladite membrane de fibres creuses définit des pores ayant des seuils de rétention des molécules d'au moins 50.000 daltons.

7. Instrument de traitement de sang selon la revendication 1, dans lequel ladite membrane de fibres creuses définit des pores ayant des seuils de rétention des molécules compris entre 50.000 et 6.000.000 daltons.

8. Instrument de traitement de sang selon la revendication 1, dans lequel ladite membrane de fibres creuses transmet l'albumine de manière sélective par rapport aux protéines plus grandes.

9. Instrument de traitement de sang selon la revendication 1, dans lequel ladite membrane souple a un seuil de rétention des molécules de 3000 daltons.

10. Instrument de traitement de sang selon la revendication 1, dans lequel ladite membrane souple est imperméable au sang et à ses composants.


21
22
20
16
30
39
33
34
42
41
32
40
43
31
46
47
34
26
23
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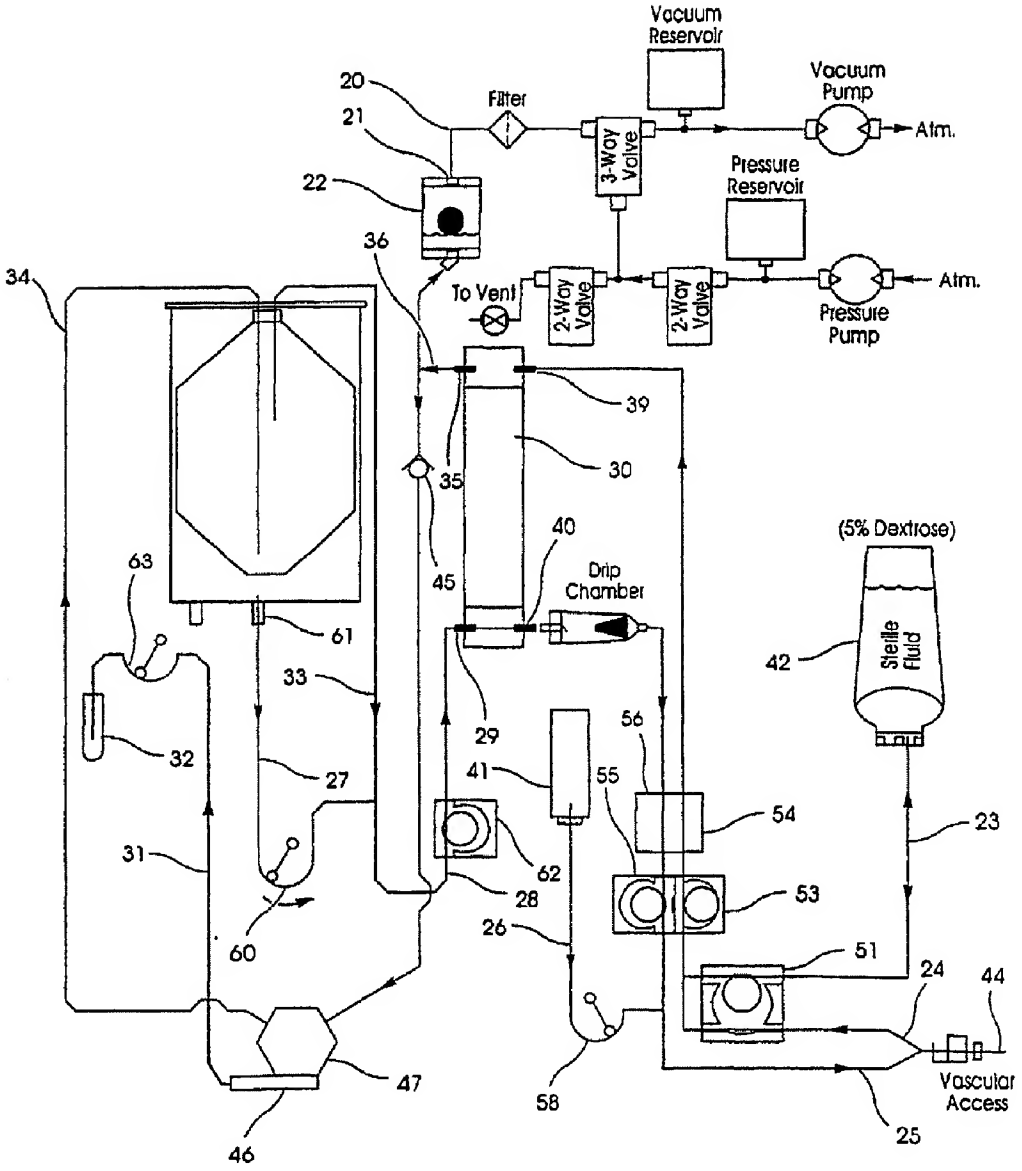
37
38
57
15
28
33
24
44
27
25
50
64
13
56
63
54
59
61
52
62
58
53
55
51
12
Utility Cart
Vacuum Tube
60
Pressure Tube
17

Fig. 1


Vacuum Reservoir
Vacuum Pump
Atm.
Filter
3-Way Valve
Pressure Reservoir
Atm.
To Vent
2-Way Valve
2-Way Valve
Pressure Pump
(5% Dextrose)
Sterile Fluid
Drip Chamber
Vascular Access
20
21
22
34
36
39
30
35
45
40
63
61
33
29
56
41
55
54
23
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44
60
47
58
25
46

Fig. 2

Fig. 3A

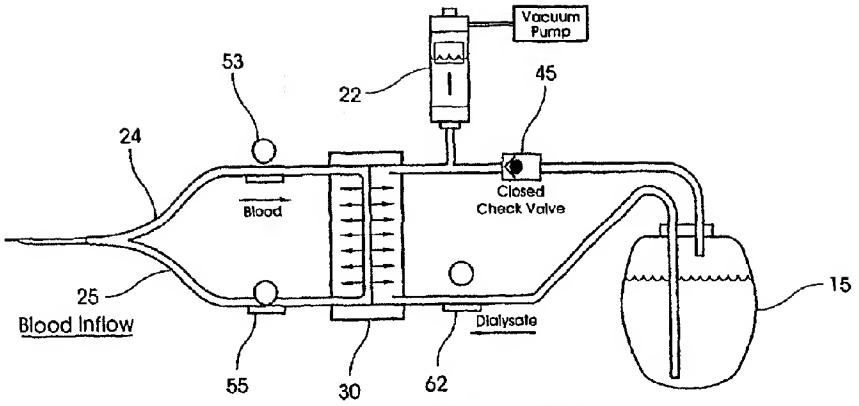
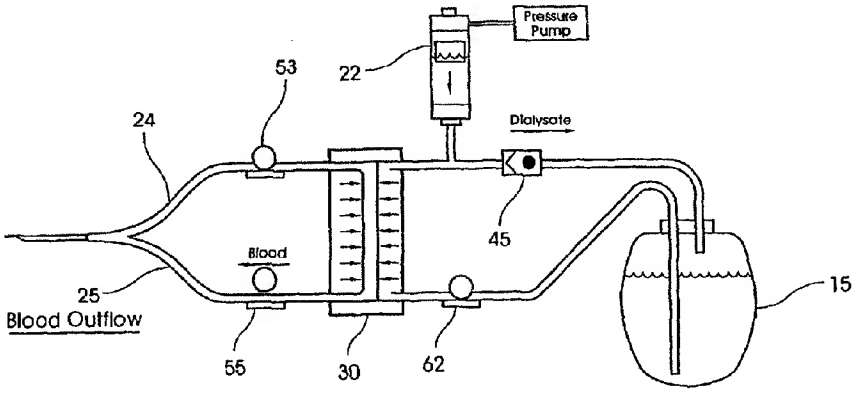

Vacuum Pump
53
22
45
24
Blood
Closed Check Valve
25
Blood Inflow
15
55
30
62
Dialysate

Fig. 3B


Pressure Pump
22
53
Dialysate
24
45
Blood
25
Blood Outflow
15
55
30
62

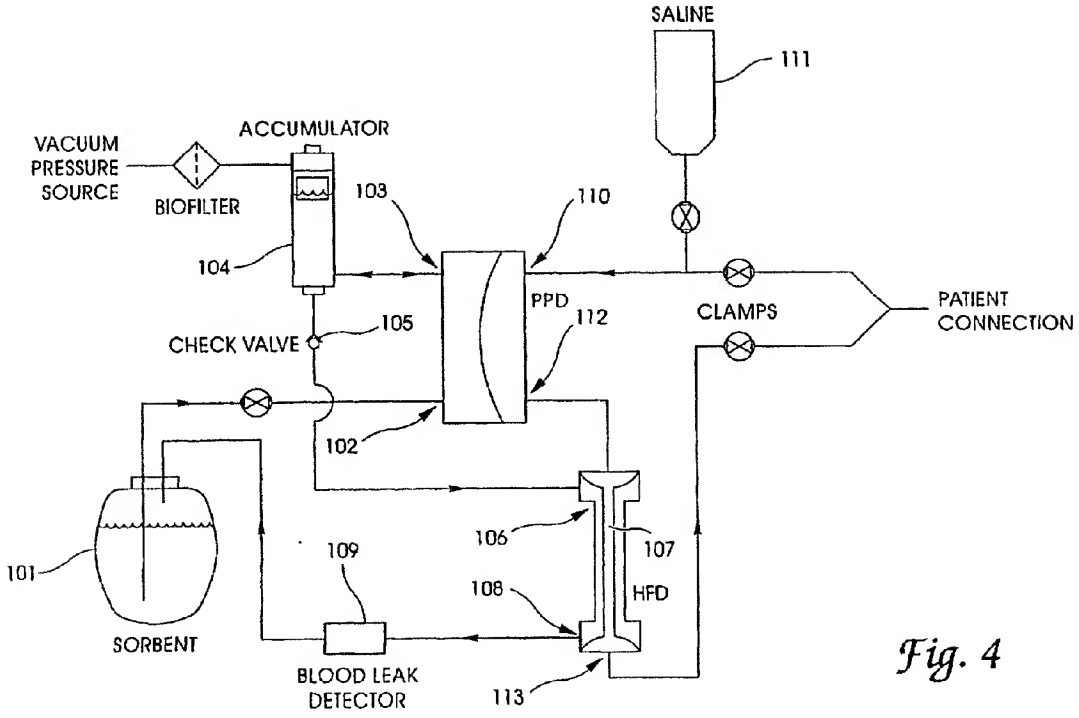

SALINE
111
ACCUMULATOR
VACUUM
PRESSURE
SOURCE
BIOFILTER
103
110
104
PPD
112
CLAMPS
PATIENT
CONNECTION
CHECK VALVE
105
102
106
107
HFD
101
109
108
SORBENT
BLOOD LEAK
DETECTOR
113

Fig. 4

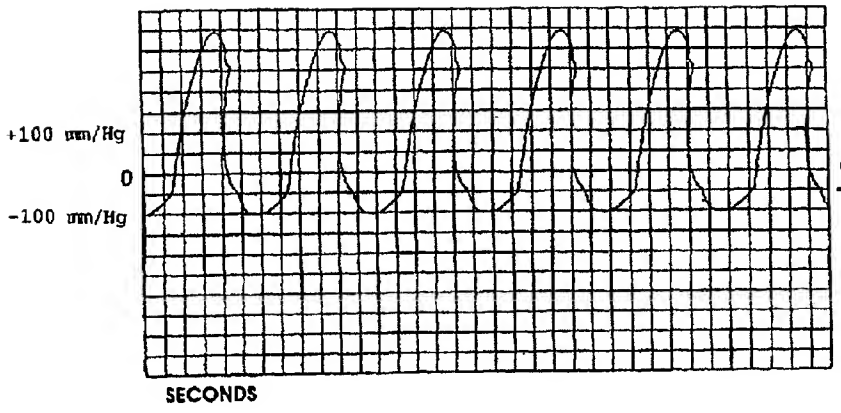


Fig. 5a

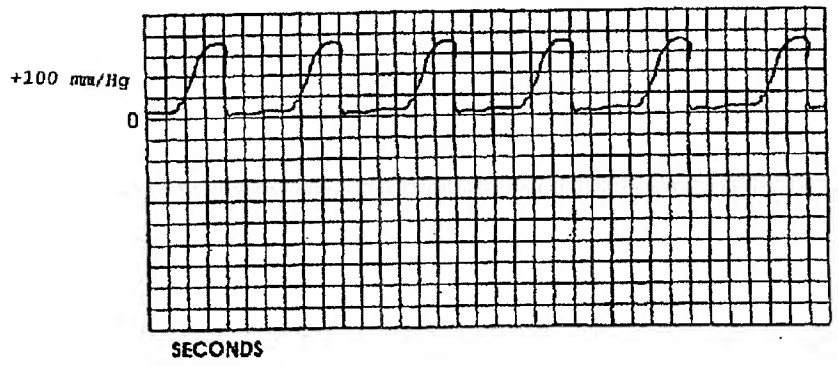


Fig. 5b

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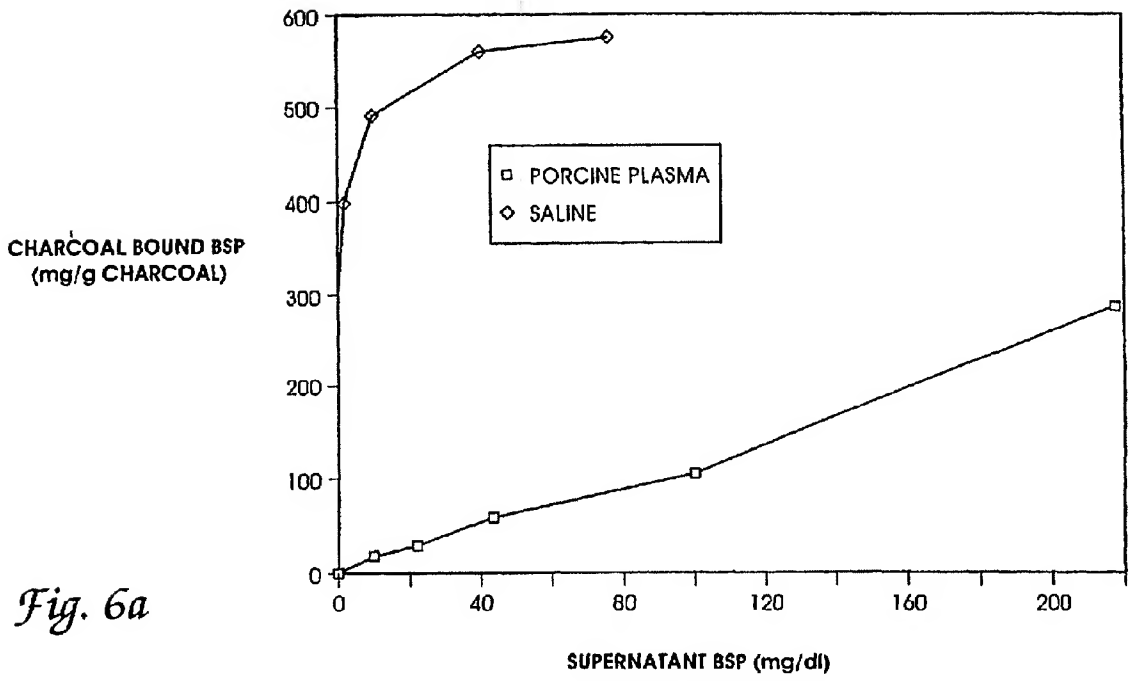
CHARCOAL BOUND BSP
(mg/g CHARCOAL)
600
500
400
300
200
100
0
0
40
80
120
160
200
PORCINE PLASMA
SALINE
SUPERNATANT BSP (mg/dl)

Fig. 6a

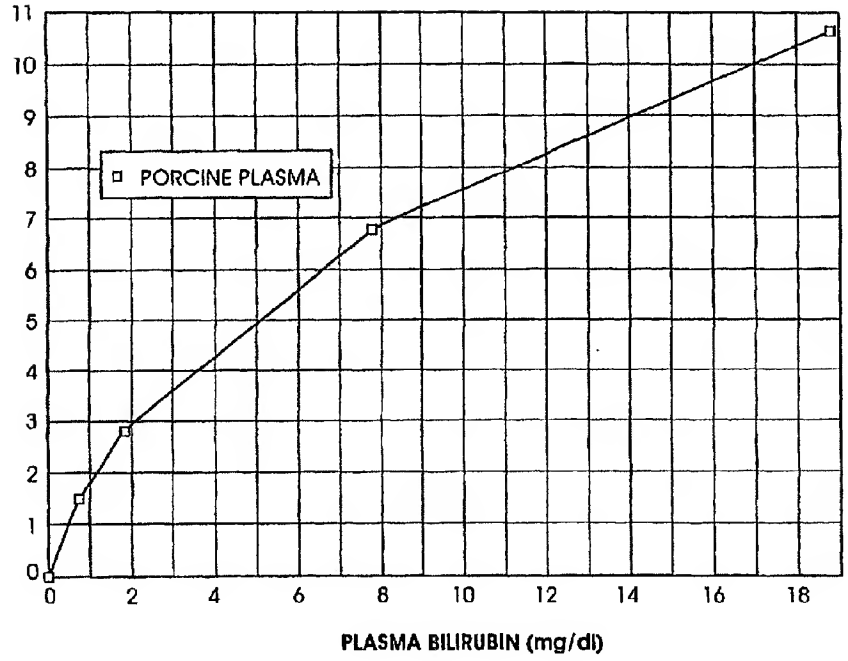
BILIRUBIN BOUND
(mg/g CHARCOAL)
11
10
9
8
7
6
5
4
3
2
1
0
PORCINE PLASMA
0
2
4
6
8
10
12
14
16
18
PLASMA BILIRUBIN (mg/dl)

Fig. 6b